REMARKS

In the Office Action dated January 15, 2003, claims 49-50, 66-67, 85 and 120-152 are pending. The Examiner states that claims 137-152, drawn to immunogenic compositions and methods of inducing an immune response in an individual, are withdrawn from consideration as allegedly directed to a non-elected invention. Claims 50, 122, 124, 129 and 134 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 49-50, 66-67, 85 and 120-136, drawn to vaccine compositions and methods of vaccination, are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

A telephone interview was conducted by the undersigned with the Examiner (Examiner Parkins) and his supervisor (Examiner Housel) on March 18, 2003. Applicants, through the undersigned, wish to thank the Examiner and his supervior for the courtesy and assistance extended on behalf of the Applicant during the interview.

During the interview, Applicants' representatives requested rejoinder of the non-elected claims, which were added in connection with the filing of the Request for Continued Examination ("RCE"). The Examiner indicated that these claims would be rejoined upon receipt of the next amendment. The Examiner also indicated that claims directed toward immunogenic compositions comprising the HIV-1 nef-deletion mutants had satisfied the enablement requirement. However, the Examiner stated in the interview summary that claims reciting immunization methods may still present enablement issues, allegedly because the disclosure does not appear to support an application of an immunogenic composition other than for the treatment and prevention of HIV-1 infection. However, the Examiner stated that the disclosure may support other immunization applications that would not be subject to the same enablement criteria as vaccine claim language. For instance, the disclosure may support the immunization of macaques or rabbits with the claimed compositions to generate antisera that would prove useful

as diagnostic reagents. The Examiner suggested that the disclosure be perused for additional support for the use of attenuated HIV-1 isolated in applications other than HIV-1 vaccine development.

Applicants respectfully submit that the presently claimed immunogenic compositions and methods of immunization simply recite that the HIV-1 isolate employed in the compositions and methods induces an immune response in the individual administered with such isolate. Such immunogenic compositions and methods of immunization are clearly supported by the specification. See, e.g., page 6, line 5; page 16, line 7-10; and page 84, lines 15-27. In particular, the specification discloses at page 84, lines 15-27, that mutant isolates are given to primates to analyze the cellular and humoral immune response induced by such mutant isolates. Where a mutant isolate induces an immune response, e.g., in an infected macaque, such macaque can be further challenged with a wild type virus.

Insofar as the immune response is induced by the immunogenic composition for the purpose of protecting the individual against an HIV-1 infection, Applicants respectfully submit that the specification provides enablement for such immunogenic compositions and methods, as well as for vaccine compositions and vaccination methods, which is addressed hereinbelow in connection with the enablement rejection of claims 49-50, 66-67, 85 and 120-136.

Claims 49-50, 66-67, 85 and 120-136 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

The Examiner has identified various literature references including Kirchof et al., Huang et al., Michael et al. and Terwillinger et al., which allegedly suggest that alterations in the *nef* gene may not be a common basis for the absence of the progression of HIV infection or AIDS. The Examiner also contends that the specification does not provide adequate guidance

concerning the selection of allelic variants of nef that contain the requisite phenotypic properties. In particular, the Examiner is concerned with the fact that the SBBC patients were all infected with the same parental virus and questions the applicability of the findings based on the same parental virus to other HIV-1 isolates. In addition, the Examiner alleges that the specification fails to demonstrate that the instant non-pathogenic HIV variants would mount an efficacious humoral or cellular immune response resulting in the prevention or treatment of HIV-infection and the clinical sequelae leading to AIDS.

Regarding the literature references which appear to suggest that alterations in the *nef* gene may not be a common basis for the absence of the progression of HIV infection of AIDS, Applicants submit that the conclusions of these references and the underlying data are highly inconclusive, even speculative. Moreover, that other mechanisms may influence the pathogenicity of HIV-1 is expected considering the complexity of the HIV genome and the interaction between virus and host. However, none of the observations made in these references negate the finding of the present invention, i.e., alterations in a particular region of the *nef* gene or LTR clearly result in the non-pathogenicity of the exemplified HIV-1 strains and such non-pathogenic strains can be used as immunogens in vaccines and immunogenic compositions against HIV infections.

Regarding the Examiner's concern of the applicability of the present findings based on one parental virus, Applicants submit that six recipients infected with the same parental strains have not exhibited AIDS symptoms over extended periods of time. Thus, it is respectfully submitted that the deletions in the present HIV-1 isolates offer a consistent basis of attenuation which is clinically measurable on live individuals. Furthermore, Applicants respectfully submit that the HIV-1 isolates employed in the present compositions and methods

are not just any mutant HIV-1 isolate, but those specifically delineated in the claims as containing "a genomic deletion in the region corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat". In the dependent claims, e.g., claim 122, such deletion encompasses at least 10 nucleotides in the specified region. Therefore, Applicants respectfully submit that the nonpathogenic properties of the HIV-1 isolates, as recited in the present claims, are adequately supported by the specification.

As to whether these HIV-1 isolates can effectively mount an immune response, Applicants previously submitted two articles, Dyer et al. (*J. Virol. 73*: 436-443, 1999) and Kent et al. article (*Journal of Virology* 75:11930-19934, 2001), as support of the enablement of the claimed subject matter.

In the study conducted by Dyer et al., the donor (D36) and the six recipients were studied for HIV-1 specific cytotoxic T-cell activity by four techniques. Four (D36, C18, C49, C98) of the seven had strong anti-HIV-1 cytotoxic T-cell responses, and one (C135) had no detectable response. It is also known (although not reported in this paper) that all SBBC members, except C135, had strong antibody responses. These results clearly evidence the effectivenss of the Sydney Blood Bank Cohort (SBBC) strain of HIV-1 in stimulating an immune response in **human** subjects.

PROTECTIVE? NOT DEMONSTRATED. SBBC COHORTS ARE DEVELOPING AIDS.

The Examiner has argued in the Office Action that two of the seven patients had weak CTL responses and one had no detectable HIV-specific CTL response, and that the authors suggested vaccine candidates would require further attenuation.

Applicants do not dispute the fact that the presently claimed immunogenic compositions and vaccines may not be perfect. However, Applicants are not, and should not be, required to show the efficacy of the subject compositions in every individual tested. Especially

in the field of AIDS where a vaccine is lacking, a showing that four out of seven patients had strong CTL responses and six out of the seven patients also had antibody responses is strong evidence that the subject compositions have sufficient immunogenicity and can mount effective immune responses in the individuals administered with such compositions.

Applicants also respectfully submit that the Kent et al. article provides evidence of the effectiveness of the non-pathogenic HIV-1 isolates employed in the presently claimed methodology and compositions. Kent et al. reported that SIV constructs, which mimick the HIV-1 constructs disclosed in the present application having a deletion in the *nef*/LTR region, protected monkeys from challenge from virus infections.

In the Office Action, the Examiner has argued that Kent et al. cannot be properly relied upon to demonstrate that the disclosure was enabled at the time of filing. In addition, the Examiner has argued that even if this reference could be relied upon, the results achieved with the SIV macaque model cannot be extrapolated to humans. Furthermore, the Examiner contends that the SIV constructs employed by Kent contained multiple deletions in both the 5' LTR and 3' nef/LTR, as opposed to the instantly claimed construct containing a single nef mutation.

In the first instance, Applicants respectfully submit that the law does not preclude submission of post-filing data which demonstrate that the claimed invention functions in the manner described. In particular, Applicants direct the Examiner's attention to the fact that the techniques employed by Kent et al. in determining the protective effects of the attenuated SIV isolates, including those for measuring the level of plasma SIV RNA and the level of CD4+ lymphocytes techniques, were all available to those skilled in the art at the time the present application was filed.

Moreover, contrary to the Examiner's allegation, it is observed that the attenuated SIV isolates employed by Kent et al. are analogous to the non-pathogenic HIV-1 isolates taught in the present specification – that is, the attenuated SIV isolates all contain a deletion in the 3' nef-LTR region (two of the four SIV isolates contain an additional deletion in the 5' LTR region). The HIV-1 isolates, as recited in the present compositions and methods, comprise a deletion in the 3' nef-LTR region. There is no limitation that the subject HIV isolates contain only a deletion in the 3' nef-LTR region.

Even with the SIV construct containing a single deletion in the 3' nef-LTR region, one of the two monkeys vaccinated with such construct was protected from a high peak level of SIV viral load as seen in the control monkeys. In addition, two monkeys vaccinated with the SIV construct containing an additional deletion in the 5' LTR region were both protected from a high peak level of SIV viral load as seen in the control monkeys.

Applicants recognize the Examiner's argument that results achieved with animals models alone may not be sufficient to satisfy the enablement requirement. However, the present specification discloses that the cohort members who all received a transfusion from a common donor having a subject non-pathogenic HIV-1 isolate are free of AIDS symptoms for extended periods of time. As discussed above, most of these individuals had either HIV-specific CTL response or antibody response. These observations, made with **human** individuals, together with the macaque data reported by Kent et al., are evidence in support of the enablement of the claimed compositions and methods.

In view of the foregoing, it is respectfully submitted that the present claims to immunogenic compositions and vaccine compositions, and immunization and vaccination

methods, are fully enabled by the specification. Therefore, the rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claim 50 is rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for reciting "humans and primates". The Examiner states that the term "primates" encompasses monkeys, apes and humans.

In response, Applicants have amended claim 50, as well as claims 125, 130, 135, 138 and 146 to delete the term "humans", and have added claims 153-158 to further delineate "primates" as "humans". As such, the rejection of claim 50 as allegedly indefinite is overcome and withdrawal thereof is respectfully requested.

Claims 122, 124, 129 and 134 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for reciting "about 10 nucleotides".

Applicants respectfully submit that the rejected claims recite "at least 10 nucleotides" and do not include the term "about 10 nucleotides". Applicants direct the Examiner's attention to the §1.116 Amendment dated February 14, 2002, which was entered according to the Advisory Action dated April 10, 2002. Therefore, withdrawal of the rejection of 122, 124, 129 and 134 under 35 U.S.C. §112, second paragraph, is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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